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July 19, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane – Room 1061
Rockville, MD 20852

RE: Docket No. 98D-1171
Draft "Guidance for Industry: For Platelet Testing and Evaluation of Platelet Substitute Products"

Dear Sir or Madam:

Baxter Healthcare, Fenwal Division is submitting the following comments to the draft guidance document, "Guidance for Industry for Platelet Testing and Evaluation of Platelet Substitute Products". In addition, please consider the following comment to Page 3, paragraph 1:

"(i.e., prior to submission of an Investigational New Drug Application...)"

FDA should clarify this statement by making clear that clinical evaluation of new platelet products can be satisfied under either IND or Investigational Device Exemption (IDE) requirements.

We appreciate the opportunity to provide comments and thank you for taking them into consideration.

Should you have any questions, please contact Adele Shoustal at (847) 270-4382 or by fax at (847) 270-2886.

Sincerely,

Marjorie D'Haeseleer

for Steven B. Binion, Ph.D
Vice President, Regulatory Affairs
Fenwal Division

98D-1171

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Guidance for Industry for Platelet Testing and Evaluation of Platelet Substitute Products

FDA CBER

May, 1999

RESPONSE FROM BAXTER HEALTHCARE

Prepared in conjunction with
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July 19, 1999

This document is intended to identify and address issues related to the Guidance for Industry for Platelet Testing and Evaluation of Platelet Substitute Products.

It is stated that the listed tests are guidelines for evaluating platelets subjected to novel technologies. The FDA correctly states that although it may not be feasible or appropriate to conduct all tests prior to submission of an IND or IDE, a reasonable number of tests that look at different aspects of platelet function is desirable. Baxter recommends that a selection of assays chosen from each of the three categories listed be considered. Baxter believes that not all tests should be required, and those that accomplish the same goal should be considered equivalent. This would avoid duplication and expense. For example there are several assays listed under platelet activation markers (see below). Perhaps one or two should be required, but surely not all of them. Furthermore Baxter respectfully notes that the FDA's own document states that it may not be feasible or appropriate to conduct all tests listed. Baxter agrees with the FDA that it would ~~be~~ unwise to completely remove any of the A, B or C paragraphs under Section III. Paragraph D is somewhat separate, however, and should be discussed subsequently. Indeed, Baxter believes that the Guidance document should be divided into two separate monographs, one on Guidance for intact human platelets and the other Guidance for platelet substitutes. The former area, intact human platelets, is better studied and much data exist in the literature. The latter on platelet substitutes is still a largely unexplored area with far more questions being raised, than are answers being provided.

I. INTRODUCTION:

Baxter notes that staff at FDA intend to replace the guidance document which was published in July - October, 1981. These new guidelines will form the basis for evaluating all further platelet and platelet substitute submissions by manufacturers to the FDA. Accordingly, Baxter believes the best course of action is for the FDA to ensure that the most appropriate, reliable, reproducible and representative assays are required, but that additional assays, which will serve no useful purpose, are not required. The ability of multiple sites to achieve the same results would make some assays preferred over others which might be more technique-sensitive. For example, serotonin uptake studies are harder to perform than CD62P activation assays by flow cytometry or measurement of β-TG. Alpha granule measurements (CD62P) would give results similar to those found for dense granules (serotonin), but with far more reproducibility and less site-site variability.

II. BACKGROUND:

Since the FDA does not favor any particular platelet assay, a battery of tests as suggested would appear to be the most appropriate method of analysis. This is commensurate with Baxter's approach to platelet storage studies over the years. However, it would be useful, if possible, to minimize the number of tests required in each area, as this directly translates into increased research costs which then reflects final pricing once licensure is received. It is noted that the radiolabeled platelet survival study is stated to be the gold standard for evaluation of clinical platelet efficacy.

III. SPECIFIC RECOMMENDATIONS:

A. In vitro Evaluation of Platelet Biochemistry and Function

Baxter agrees that the BEST task force review on platelet testing is an excellent document. Basically, this document describes a large series of in vitro assays which are used, or recommended to be used, by various manufacturers or researchers for evaluation of platelets. Although this document is quite comprehensive, the assays listed in the Guidance Document under current discussion, would appear to serve as a more reliable and focused source of which assays the FDA is likely to request in 2000 and beyond.

Platelet Enumeration: There should be a separate section on platelet enumeration using particle or laser counters. The determination of an accurate platelet count is critical for all such platelet work and should be given separate status.

Morphology: Baxter agrees that light microscopy is desirable and necessary. However, the section should state that the morphology should be performed with a phase microscope using at least a 100x lens. Baxter, however, believes that there should not be a requirement for electron microscopy (EM). Baxter does recommend that EM be categorized as a supplemental test which could be provided as, and if, necessary. It definitely should not be a requirement for all platelet studies. Baxter believes that the Extent of Shape Change (ESC) assay does correlate with in vivo survival and should be included in this section on morphology, and ESC or morphology by light microscopy data should be provided with any licensure submission data.

Biochemical Status: The FDA lists a variety of in vitro tests to be evaluated and correctly notes that these assays generally do not correlate with in vivo recovery and survival. They recommend measuring levels of ATP, glucose and lactate as well as lactate dehydrogenase and pH. Baxter has not routinely recommended that its investigators measure levels of platelet ATP for most of its product licensure submission data. Although some researchers feel that ATP is important, because of a lack of a clear correlation of ATP levels with in vivo performance, Baxter is not in favor of requiring this assay. However, it is admitted that this would be a fairly simple assay to perform, as kits are available for this. However, here is an example of a test Baxter feels is not necessary, and does not correlate with in vivo recovery and survival. To just include it because it could be measured would add little to product evaluation but could unnecessarily increase the cost of performing a study. Baxter does recommend that Glucose and Lactate be routinely performed, with data points gathered over several storage days. The LDH and platelet count are both measures of cell lysis and Baxter agrees ~~with~~ these assays.

Under pH, Baxter is pleased to note that the FDA for the first time states that a pH below 6.2, (not 6.0) correlates with decreased in vivo performance. Baxter believes that this move by the FDA should be applauded. Baxter is also pleased to note that for the first time (as far as Baxter is aware) an upper limit of alkalization of the platelet poor plasma is also mentioned (pH 7.6). We believe that these parameters of pH 7.6 and pH 6.2 are reasonable. Indeed, Baxter might recommend that the pH on the lower end be raised up a bit to require a pH 6.3 or higher. However, raising the minimum pH to pH 6.2 is a

move in the right direction. Some would claim that pH 7.6 has not been shown to be harmful. However, perhaps the FDA could make a clear statement that if the pH of a unit of platelet concentrate is > pH 7.6 at the end of storage, then that unit should be evaluated by several other assays. Furthermore, if those assays are found to be out of established ranges, the quality of the platelet product produced after the manipulation being studied could be called into serious question and further studies would be indicated. Baxter would also call to the FDA's attention that they have not required blood gases and bicarbonate measurements. Although the blood gases would correlate with lactate and glucose and pH, having blood gas data, (which should include bicarbonate levels), would be very useful and Baxter would recommend their inclusion, even if only as a supplemental assay. Measure of pO_2 and pCO_2 serially over time would provided valuable data not attainable by any other method of measure. These assays are easily performed and should be expressed as a value at 25C.

Percent Platelet Activation: Baxter has evaluated CD62P for many studies over the years. Prior to this assay, β-thromboglobulin was evaluated. Baxter believes that measuring the activation of platelets using one surface marker (CD62P) is appropriate. However, we do not feel that all, or actually any of the other listed markers need be assayed. The evaluation of CD63 or the activated form of fibrinogen IIb/IIIa via PAC-1, may be of interest, but not more valuable than CD62P for these types of FDA licensure submissions. Commercial availability as well as the reliability of some of these reagents may not be as good as CD62P; PAC-1 is not likely subject to rigorous cGMP production standards, being a research laboratory reagent. β-thromboglobulin and platelet factor 4

can be measured. However, there should be an option to measure either release of β-thromboglobulin or platelet factor 4 **or** measuring percent activation of CD62P, by flow cytometry. Platelet factor 3 activity is increased with platelet activation. However, measurement of platelet factor 3 procoagulant activity is not a fully standardized assay. While an annexin V assay might be useful, it is not standardized or correlated with in vivo responses. Most probably there is no need to require these assays, unless the submission related to a platelet membrane preparation. Again, Baxter suggests that platelet substitutes, including membrane preparations be discussed in a separate Guidance Document more amenable to the experimental and research nature of platelet substitute products at this time. Annexin V would be more appropriately used in such research. Thus, for purposes of platelet activation it would be appropriate to measure only percent CD62P activation. Baxter believes the other markers should be considered optional. β-thromboglobulin or platelet factor 4 should be required if flow cytometric analysis of CD62P is not provided.

Physiologic Responses: For physiologic responses it would be appropriate to measure osmotic recovery and/or the extent of agonist-induced shape change (ESC). Most researchers believe that extent of shape change does correlate with in vivo survival. ESC is somewhat technique dependent. However, a commercial device to measure ESC is being considered for licensure. ESC is also discussed under Platelet Morphology. Baxter believes that hypotonic shock response (HSR- also known as osmotic recovery) is an excellent assay. The FDA could decide that Extent of agonist-induced Shape Change (ESC) should be performed, as well as HSR. Some laboratories perform one or the other.

If ESC is considered under morphology, the HSR then would be useful as a physiological assay. Platelet aggregation is an area that Baxter has not found to be exceptionally useful. If, however, the FDA is firm in their desire to require such an assay, Baxter suggests the Agency considers requiring the applicant to measure aggregation with one or at most two pairs of agregating agents; with one, or at the most, two concentrations of agonists. The recommended combination/concentration of agonists could be listed in the Guidance document. Baxter would recommend that a minimum number of dual agonist platelet aggregation studies be specified. Baxter does not believe that the information derived from such studies, however, would be that useful. A standard dual agonist package such as ADP/collagen, or ADP/epinephrine should suffice.

The serotonin uptake and agonist induced serotonin secretion assays are technically involved procedures. Baxter does not believe that evaluation of serotonin discharge, which evaluates dense granule characteristics, is to be preferred over the α-granule assay, CD62P. Baxter would recommend that platelet serotonin uptake not be required. Most centers cannot perform the technically tricky assay. It is useful as a research study only and does not correlate with in vivo survival. Serotonin uptake and secretion are involved, technique-sensitive assays. Agonist-induced expression of platelet activation markers such as using thrombin-related activation peptide (TRAP) to stimulate CD62P, while useful is not well correlated with in vivo survival and Baxter does not recommend its use for licensure submissions.

Quantitation of Microparticles: Baxter would recommend that the quantitation of microparticles not be routinely required for individual protocols unless microparticle formation plays a major role in the product production, such as in a platelet membrane-derived product. This assay is difficult to performed and is appropriately analyzed quantitatively by using flow cytometry or other techniques. However, it is difficult for many labs to quantitate microparticles as it entails a great deal of subjectivity in data interpretation. In addition, there is no standardized assay for counting microparticles – any assay used would need to be validated among all sites participating in a study. Baxter believes there is no need to evaluate generation of microparticles for every blood component processed; it should be reserved for research purposes. At a minimum, clarification of this section is needed. Unless it is clearly shown that platelets are fragmented by the process under study, and that microparticles are likely formed, (preferably as shown by increases in LDH or decreases in platelet count, for example), Baxter would not recommend including platelet microparticle determination as part of a laboratory evaluation of say, the effects of a new plastic bag or a new blood filter on stored platelets. This assay should again, be relegated to the separate Guidance Document recommended for analysis of platelet substitutes; quantitation of microparticles is not a standardized assay.

Comments: It is noteworthy that the FDA has stated that platelet studies should be run as a paired comparison with identical storage conditions. The Agency makes the specific point that if an alternative storage medium, other than plasma is used, in vitro test conditions should mimic in vivo conditions. That is, if non-plasma additives such as

PAS- III are used to store platelets, and for a comparison they are resuspended in plasma for testing, the resuspending plasma should be equivalent to the plasma used for storage. This is a very important point and should not be ignored. Baxter notes that this point is reflected in a recent publication by Mondoro TH, Shafer BC; and Vostal JG. Restoration of In Vitro Responses in Platelets Stored in Plasma. Amer J Clin Pathol. 1999;111:693-9. In this paper, the authors conclude that for direct comparison of platelet responses following novel storage methods, the resuspending plasma must be stored under the same conditions as the plasma used for the control platelet units. Baxter will be aware of this issue during future studies involving platelets.

B. Platelet Survival in the Circulation:

The most critical aspect of this section relates to the statement by the FDA that the design of radiolabeled survival studies preferably should be a double labeling technique. It is stated that recent advances in double labeling of platelets with 111-indium and 51-chromium for simultaneous comparison in a single recipient, provide satisfactory data with less scatter in data points. The next sentence states, that extent of data scatter will determine the number of volunteers needed to be tested. Thus, it would appear that unless paired radiolabeled survival studies with indium and chromium together are performed, a larger "n" likely will be needed. The number of centers that can perform dual labeling with 111-indium and 51-chromium, however, are relatively few. The need for double labeling of platelets simultaneously, while preferred, should not be required. Performing two independent sets of indium-111 labeling, (pre and post technique) should be acceptable as it has been for many years. Baxter agrees, however, that this would mean

that a larger additional sample population would be needed. All seems to be dependent on the scatter in the sample population data. It is clearly stated that prior to performance of radiolabeled in vivo survival studies, in vitro assays need to show no significant changes. Thus, the FDA plans to continue its concept of a three phase evaluation schema:

1. in vitro evaluation
2. in vivo radiolabeled assays in volunteers
3. patient transfusion studies

Baxter agrees with this approach.

C: Clinical Hemostatic Efficacy: The FDA states that there are no adequate clinical tests to demonstrate platelet efficacy. They state that bleeding time has been shown to lack correlation even within a single patient and imply that clinical surrogate endpoints have only related to increases in corrected count increments and in platelet counts of over 20,000/μL. The FDA clearly states that there is an assumption that a sufficient number of circulating platelets will offer adequate protection. The Agency then makes a very substantive statement that clinical performance (efficacy) of platelets obtained with novel product technologies should be evaluated by inclusion of these platelet products in clinical practice. Records of hemostatic effectiveness, clinically defined by changes in epistaxis, hematuria, and/or petechiae should be included as part of the IND application.

Baxter interprets the FDA as saying that the type of evaluation such as is being performed by Baxter/Cerus for the S59 Platelet Study is what will be expected in the future. Intensive clinical evaluations for changes in bleeding would seem to be required.

Potentially use of the WHO bleeding severity scale might be necessary, if FDA considered it to be an acceptable standard scale by which to evaluate cessation of clinical bleeding. Thus, it would appear that the FDA will no longer accept only corrected count increments (CCIs) and/or bleeding times as adequate evidence of clinical hemostatic efficacy. Although they do state that bleeding times may be submitted as additional data. Therefore, Baxter (and all manufacturers) could be facing the potential requirement to perform extensive and expensive studies to show that platelets prepared by the process under study, are hemostatically efficacious. Presumably these studies would be on a somewhat smaller level than that at which the Baxter/Cerus S59 Platelet Study is being performed. Corrected count increments likely will be required, but alone, are insufficient. This is a major area and the FDA is asked for clarification on this point. Baxter recommends that such an involved and extensive evaluation only be required for products undergoing substantive processing and not for platelets exposed to devices subjected to only minor changes in product improvement, such as an improved blood filter. The effects on platelets of a major processing change such as S-59 psoralen treatment, however, should be more fully evaluated.

D. Evaluation of Platelet Substitutes: Again, Baxter recommends that this section be split off into a separate Guidance Document. Here the FDA makes important comments regarding evaluation of substitutes. The Agency talks about platelet substitutes emulating a single aspect of normal platelet function and the difficulty in evaluating efficacy, both in vitro and in vivo. Baxter agrees with the Agency's opinion in recognizing the possible limited use of a platelet substitute, and that the substitute need not replace ALL known

platelet functions. The FDA alludes to the ability of some platelet substitutes to decrease the bleeding time in Dr. Blajchman's thrombocytopenic animal model. Further, as noted above, the FDA states that it is possible that various platelet substitutes may replace only a specified aspect of total platelet function, but that this aspect should clearly be defined and clinical benefit tested accordingly. The FDA also states that it may be possible to approve platelet substitutes for short-term use or long-term use. Baxter supports the FDA's position that platelet "debris" or fragments need not necessarily be able to recreate an intact functional platelet.

Baxter notes, however, that only some investigators may be able to measure changes in skin bleeding time or stool blood loss. Baxter recommends that the Agency not require such studies for licensure of all platelet substitutes. Such a requirement would clearly have an impact on a manufacturer's clinical trial site selection, since relatively few sites could or would perform such studies. This approach helps focus on what the new product might be able to do without worrying about what it can not do. Regardless, it is clear that the amount of evaluation needed for licensure of platelet substitutes, clinically, will be extensive. Performing skin bleeding times (please note the prior FDA comments in the Guidance document that skin bleeding times were essentially worthless), platelet counts, or measuring radiolabeled red blood cell loss in the stool of stable aplastic thrombocytopenic patients is no simple feat. All of these assays require a fair amount of dedication to complete, and not many sites would have a large population of aplastic thrombocytopenic patients who would be willing to undergo bleeding times and radiolabeled stool collections. Radiolabeled red cell loss in the stool is a technology that

primarily Sherril Slichter has performed. Whether these assays could be performed at multiple other sites is something that other manufacturers will need to consider. Baxter requests clarification from FDA on these points.

Additional in vitro animal tests: These tests may be necessary to define efficacy and safety. The FDA appears to be open to suggestions in this area. Three types of evaluations are listed: (1) evaluation of prothrombotic potential involving thrombosis in normal animals and animals with DIC, (2) evaluation of immunogenicity associated with infusion of only some parts of the platelet and whether an immunogenic response is produced; it needs to be demonstrated that the substitute is not more immunogenic than the intact platelet; (3) evaluation of toxicity due to additives: in this area the product or process needs to be fully evaluated for toxicity, mutagenicity and carcinogenicity. Platelet substitutes, will be given to some recipients during their reproductive years. Thus, toxicology and teratogenic assays need to be evaluated and full disclosure made on whether additives interfere such as by adding color to plasma.

The FDA does not provide any specific suggestions and leaves this area open to the manufacturer. Baxter requests clarification of this area. Some general and specific recommendations for what the Agency considers to be acceptable toxicity studies would be helpful. It would help the field learn which types of assays would be acceptable to the FDA. Baxter then could be an advocate those assays which it believes are best able to answer the questions of safety and efficacy. Baxter believes that all companies should be

required to demonstrate such safety and efficacy evaluations as part of regulatory submissions for their products.

Final comments: The FDA Guidance document will cover a number of platelet products stored under standard blood bank conditions for treatment of thrombocytopenia. Baxter agrees that substitutes which aim to be considered as alternatives to these products should demonstrate a clear benefit:risk ratio. Thus, frivolous products should not be submitted for evaluation. The FDA has developed various guidelines for analyzing intact platelets. For platelet substitutes, the most important questions remain to be clarified and should be addressed separately from intact human platelets.

Baxter hopes that these comments have been helpful and is grateful for the opportunity to respond to the Guidance Document.

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